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Meeting  
Food and Drug Administration  
Rockville  
June 14, 2001

**One-Source Supplier for  
Enterprise Production Management**

Propack Data GmbH • Vincenz-Priessnitz-Str. 1 • 76131 Karlsruhe • Germany • [www.propack-data.com](http://www.propack-data.com)  
Propack Data Corporation • 2000 Regency Parkway, Suite 375 • Cary, NC 27511 • USA • [www.propack-data.com](http://www.propack-data.com)

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## PD - PRESENTATION TEAM

- **Christian Fortunel**  
President  
Propack Data Corporation  
phone: (919) 465 17 41 x312  
e-mail: [chf@propack-data.com](mailto:chf@propack-data.com)
- **Hermann Schaefer**  
Director Customer Services U.S.  
Propack Data Corporation  
phone: (919) 465 17 41 x313  
e-mail: [hes@propack-data.com](mailto:hes@propack-data.com)
- **Dr. Gerhard Werling**  
Director Quality Management & Validation Services  
Propack Data GmbH, Germany  
phone: +49-721-9650-835  
e-mail: [gw@propack-data.com](mailto:gw@propack-data.com)

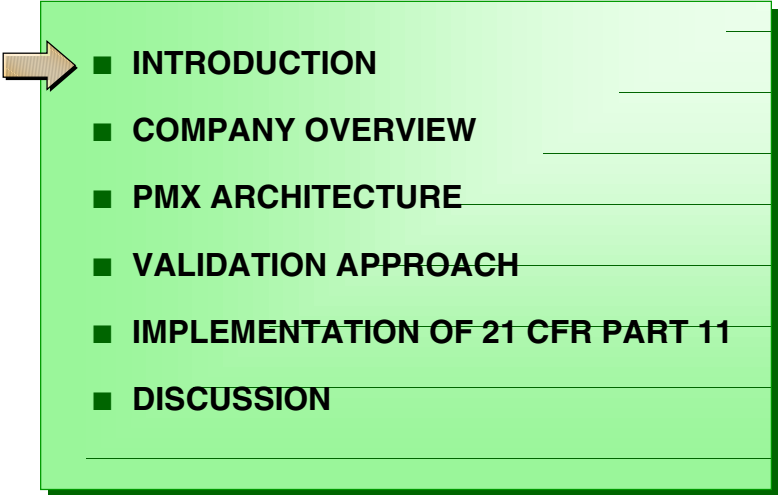
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## AGENDA

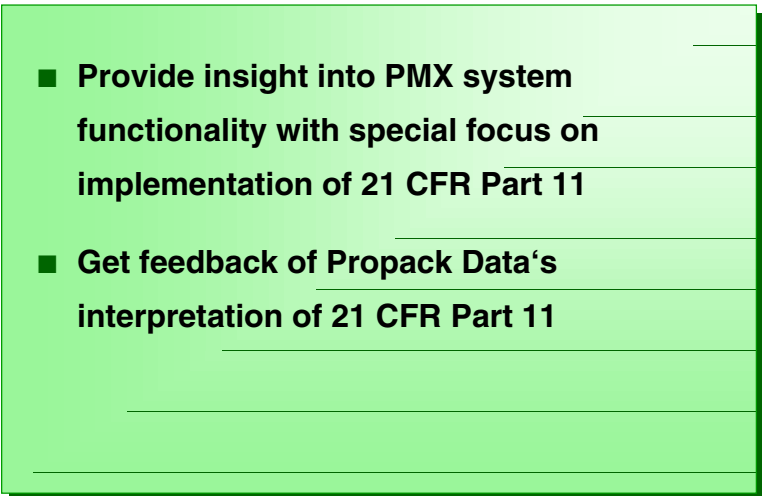


- INTRODUCTION
- COMPANY OVERVIEW
- PMX ARCHITECTURE
- VALIDATION APPROACH
- IMPLEMENTATION OF 21 CFR PART 11
- DISCUSSION

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## OBJECTIVE



- Provide insight into PMX system functionality with special focus on implementation of 21 CFR Part 11
- Get feedback of Propack Data's interpretation of 21 CFR Part 11

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## GLOBAL ACTION - LOCAL REACH

**Propack Data Corporation**   
American Headquarters  
Cary, NC, USA

**Branch Offices in**  
Parsippany, NJ  
Chicago, IL (planned)

**Propack Data S.r.L.**   
Vimercate (MI), Italy

**Propack Data Ltd.**   
Stansted/ London, UK

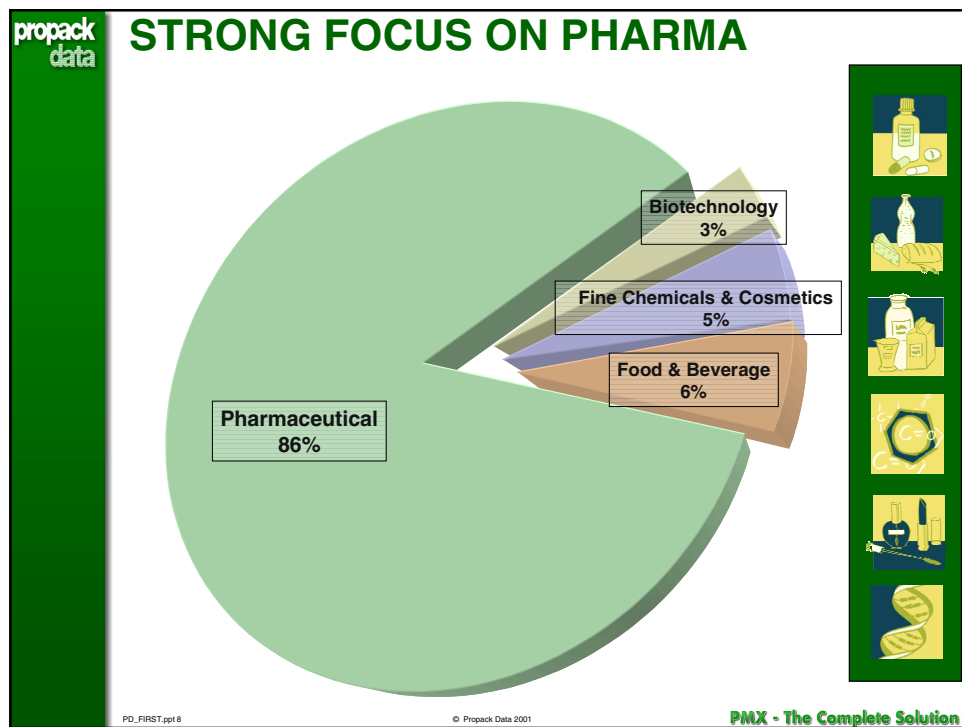
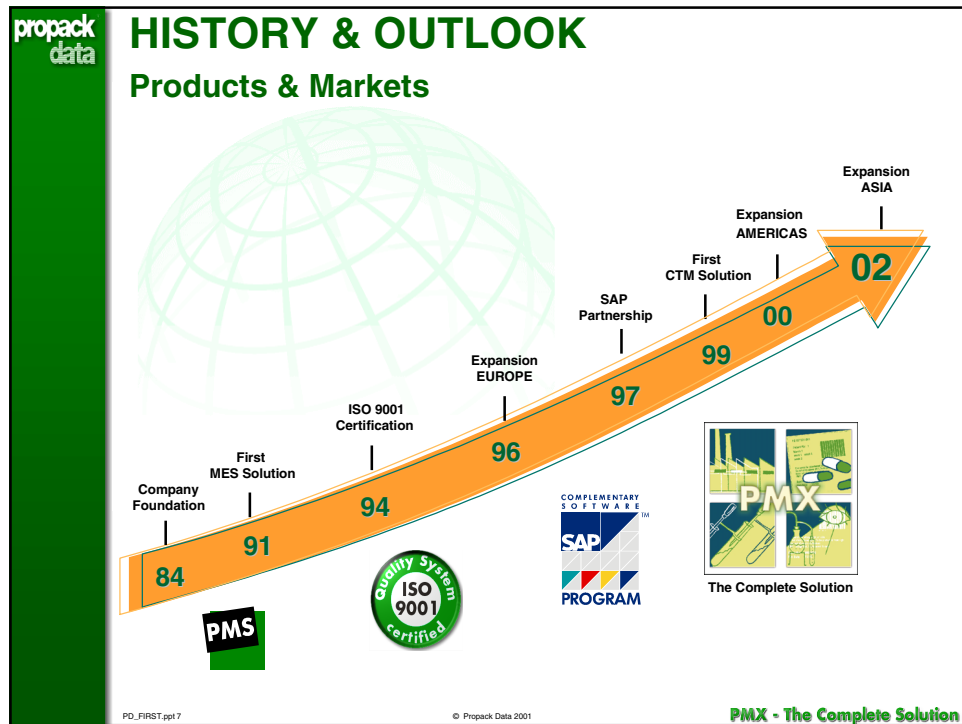
**Propack Data S.A.S.**   
Toulouse, France



**Propack Data GmbH**   
Global Headquarters  
Karlsruhe, Germany

**Branch Offices in**  
Bad Säckingen, Bad Wurzach,  
Bergisch Gladbach, Leipzig

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## PROPACK DATA - REFERENCES

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## QM CERTIFICATE & CUSTOMER AUDITS

**Since 1994  
ISO 9001 -  
Certification**

**Since 01/2001  
ISO 9001:2000  
Certification**

**CUSTOMER AUDITS - last three years**

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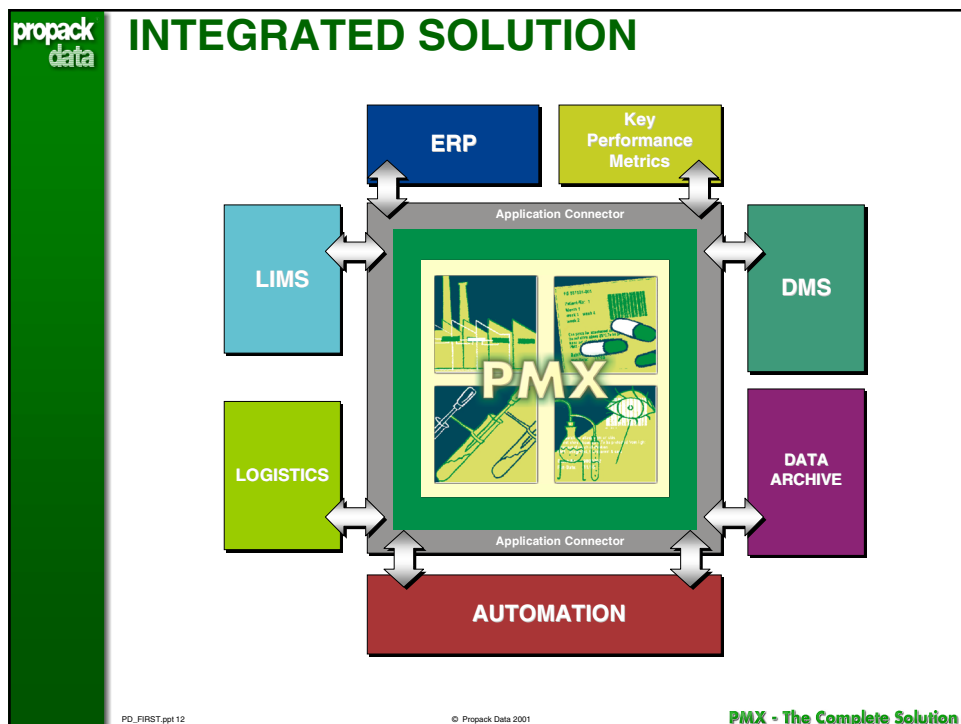
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## PMX THE COMPLETE SOLUTION

 <p><b>RDM</b></p> <p>Utmost Flexibility</p> <p>Research &amp; Development Management</p>	 <p><b>MES</b></p> <p>Paramount Efficiency and Quality</p> <p>Manufacturing Execution System</p>
 <p><b>CTM</b></p> <p>Complete Control and Overview</p> <p>Clinical Trial Management</p>	 <p><b>MQS</b></p> <p>Total Quality Management</p> <p>Manufacturing Quality Service</p>

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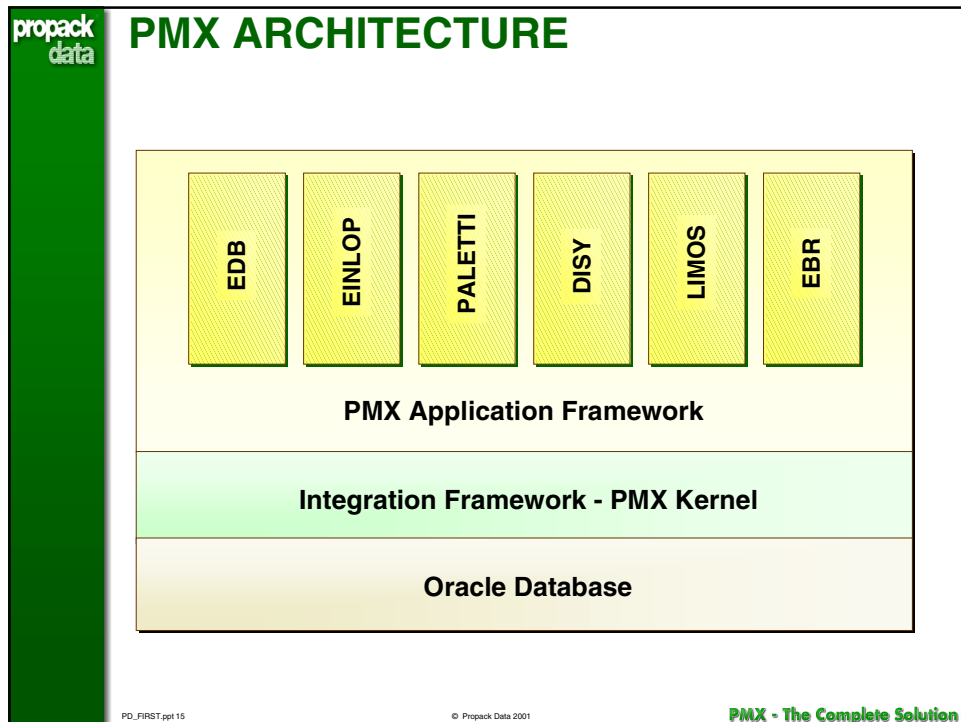
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## PMX IMPROVES cGMP COMPLIANCE

**"Improve cGMP compliance"**


Material Reconciliation	DISY
Weigh / Dispense	EBR
Authorization Control	EDB
Batch Record	EINLOP
Audit Trail	LIMOS
Controls for identification	PALETTI
Recipe Management	PDB
Sequencing of Work Flow	PEPS
Device checks	TEDIS
Material Identification	
Lot Management	
Archiving	
Reporting	
Staff Qualification	
Maintenance	

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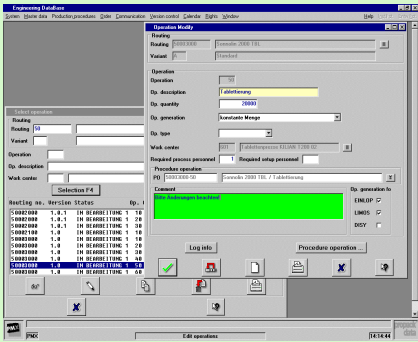
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## PRODUCTION KNOWLEDGE MANAGEMENT



### EDB

- Master data management
  - work centers
  - BOM items
  - storage
  - company and shift calendars
  - users
- Version-controlled master data
  - Master recipe procedures
  - bills of material
  - Master recipes
  - SOPs
  - Master recipe operations
- Electronic signatures
- Editor (Word-compatible)



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## ELECTRONIC BATCH RECORDING

### E B R

- Interactive HTML-based on-line process control
- Operator-related electronic signature
- Electronic link to batch processing technology via PLC, scales, process equipment
- Automated generation of the production protocol

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## PRODUCTION DATA AND BATCH ARCHIVE

### P D B

- SQL-based reporting functions
- Long-term batch archive
- External archive management
- Document scanning

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## PRODUCTION SCHEDULING & CONTROL

# EINLOP

- Electronic planning board
- Interface to ERP
- Optimal order sequencing
- Optimization of set-up times
- Resource requirements
- Personnel placement plan
- Checking of dates and resources
- Simulations
- Monitoring of order progress

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## QUALIFICATION MANAGEMENT

# PEPS

- Personnel qualification data
- Staff qualification, training administration
- Plant- / GxP- and SOP-related instructions
- Order-related placement planning
- GxP Training Management
- Trigger based deviation reporting
- Reports

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## QUALITY MANAGEMENT

### QUIBS

- GLP/FDA-compliant master data management (check plans, check items, processes, etc.)
- Process-attending in-process control during production and packaging at the work center/laboratory
- Sampling at goods receipt/issue as well as during process
- Order processing in analytic, microbiology and stability laboratories (chemical/physical and microbiological analysis procedures)
- Batch control and evaluation on the basis of research results
- Quality certificates/Certificates of analysis
- Documentation, reports
- Automatic download of check results

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## DISPENSING AND WEIGHING SYSTEM

### DISY

- Identification of containers and input materials with RF-scanners
- Recipe-based weighing
- Open scales interfaces, automation of dosage device
- Labeling, weighing protocol, batch documentation
- Integration with EBR

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## AGENDA

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Validation\_approach / 1

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## VALIDATION STRATEGY

### A TWO-STEP APPROACH

```
graph LR; A[Pre-validation of standard solution package] --> B[Validation of Customer System]
```

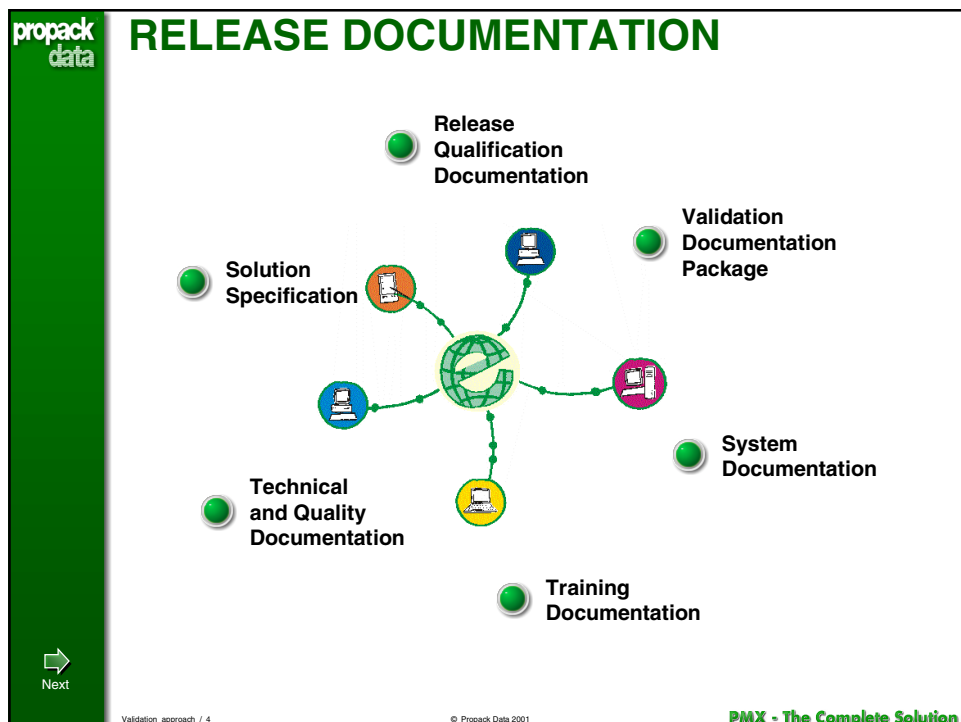
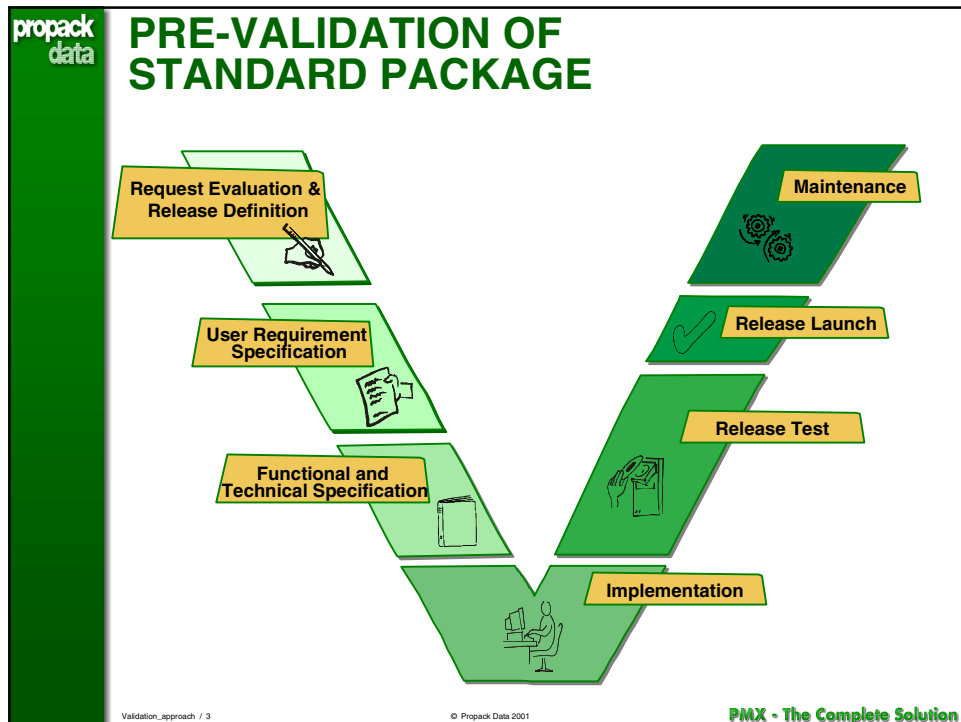
Pre-validation of standard solution package

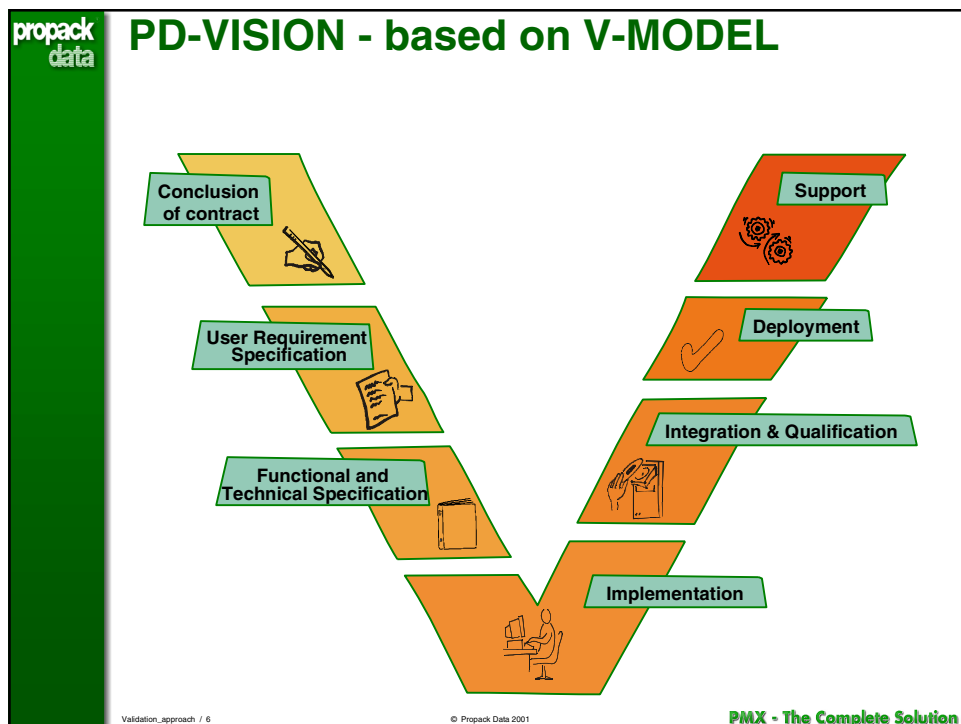
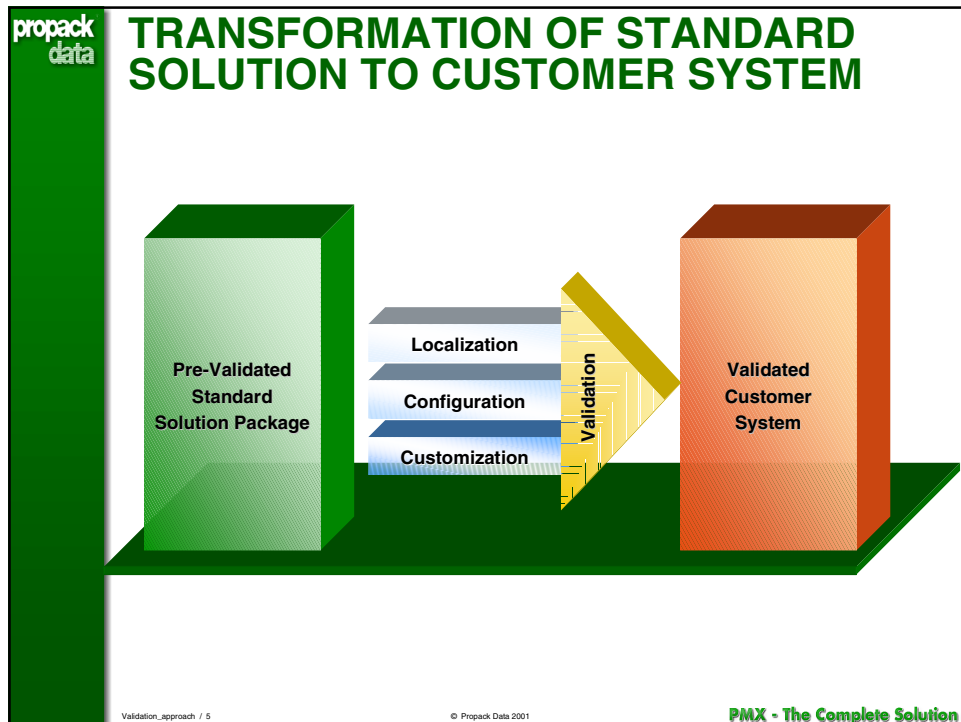
Validation of Customer System

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## TEST STRATEGY

- Test suite with phase specific test objective and low redundancy between phases
- Maximum "re-usability" of testing
- Focus on changes applied to standard software
- Test specification based on documented risk analysis to access impact of changes



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## TEST METHOD

	Software item test	System test	HW-Installation test	Interface test	Acceptance test	PQ test
<b>test object</b>	Software-Element	Function / Transaction	Hardware	Interfaces to other systems	Business processes	complete system in operational environment
<b>test strategy</b>	white box test	black box test; Challenge Tests completeness	check of functionality and Tests	black box test; Challenge process level	Challenge testing on	test in operational environment
<b>Focus</b>	Code for Change or Enhancement	New or customized Functions		New or customized interfaces	GxP - relevant processes	GxP - relevant data

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## PMX FEATURES SUPPORTING 21 CFR PART 11 COMPLIANCE

**A Selection:**

- Reporting of Electronic Records
- Authority Checks
- Archiving
- Audit Trails
- Sequencing of Steps & Events
- Electronic Signature Manifestation
- Signature / Record Linking
- Electronic Signature Components
- Controls for Identification Codes / Passwords

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## 21 CFR PART 11 REQUIREMENTS

§11.10(b)

The system shall provide the ability to **generate accurate and complete copies of records** in both human readable and electronic form suitable for inspection, review, and copying by the agency.

Implementation in PMX

- **Reporting Features**

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## 21 CFR PART 11 REQUIREMENTS

§11.10(c)

The system shall ensure the **protection of records** to enable their accurate and ready retrieval throughout the records retention period.

§11.10(d)

**Limiting system access to authorized individuals must be ensured.**

Implementation in PMX

- **User Authorization**
- **Access Restrictions**
- **Archiving Features**

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## 21 CFR PART 11 REQUIREMENTS

§11.10(e)

The system must provide secure, computer-generated, time-stamped **audit trails** to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information.

Implementation in PMX

-  **Audit Trail**
-  **Version Control**

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## 21 CFR PART 11 REQUIREMENTS

§11.10(f)

Use of operational system checks to **enforce permitted sequencing of steps and events**, as appropriate.

Implementation in PMX

-  **Sequencing of Actions**

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## 21 CFR PART 11 REQUIREMENTS

§11.10(g)

Use of **authority checks** to ensure that only authorized individuals

- can use the system,
- electronically sign a record,
- access the operation or computer system input or output device,
- alter a record, or
- perform the operation at hand.

Implementation in PMX

- **User Authorization**
- **Certifying Authorization**
- **Access Restrictions**

← →

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## 21 CFR PART 11 REQUIREMENTS

§11.50(a)

Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:

- (1) The **printed name** of the signer;
- (2) The **date and time** when the signature was executed; and
- (3) The **meaning** (such as review, approval, responsibility, or authorship) associated with the signature.

Implementation in PMX

- **Signature Manifestation**

← →

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## 21 CFR PART 11 REQUIREMENTS

§11.50(b)

Printed name of the signer, date and time, and meaning associated with the signature shall be subject to the **same controls as for electronic records and shall be included as part of any human readable form of the electronic record** (such as electronic display or printout).

Implementation in PMX

 **Management and Display of Electronic Signatures**

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## 21 CFR PART 11 REQUIREMENTS

§11.70

**Signature/record linking:**

Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that **the signatures cannot be excised, copied, or otherwise transferred** to falsify an electronic record by ordinary means.

Implementation in PMX

 **Signature / Record Linking**

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## 21 CFR PART 11 REQUIREMENTS

§11.200(a)(1)  
Electronic signatures that are not based upon biometrics shall employ at least **two distinct identification components** such as an identification code and password.

Implementation in PMX

- **Signature Components**

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## 21 CFR PART 11 REQUIREMENTS

§11.300 (b)  
The system shall provide controls ensuring that identification code and password issuances are **periodically checked, recalled, or revised** (e.g., to cover such events as password aging).

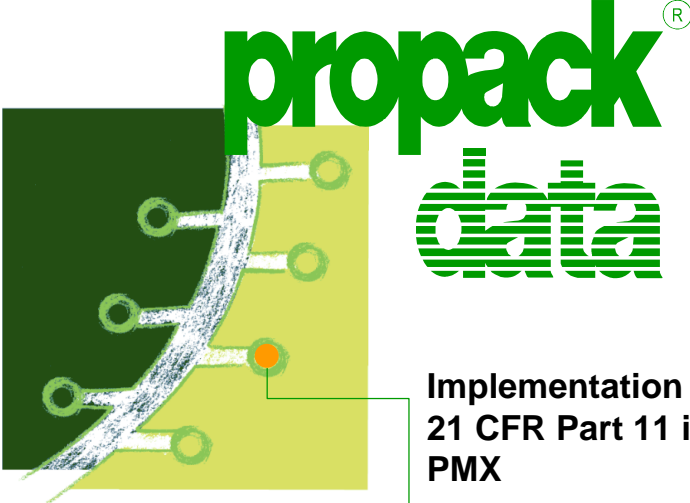
Implementation in PMX

- **Password Features**
- **Reporting for User Authorization**

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Implementation of  
21 CFR Part 11 in  
PMX



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## 21 CFR PART 11 IMPLEMENTATION

### Reporting

- Every electronic record can be generated in human readable and electronic form
- Standard templates or customized templates

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## 21 CFR PART 11 IMPLEMENTATION

### Authorization

- Two kinds of Authorizations
  - Operational Authorization - *Execution*  
The rights required by an operator for **executing** a certain function
  - Certifying Authorization - *Approval*  
The rights required by a supervisor/operator for **certifying** that the results of a certain operation are in order
- Authorizations are associated with a Customer-specific Hierarchy of User Groups and Users

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## 21 CFR PART 11 IMPLEMENTATION

### Access Restrictions

- Login Features
  - ✓ Configurable number of false Login Attempts
  - ✓ Protocol of all Login Attempts
- Password Features
  - ✓ Encrypted Storage
  - ✓ Configurable expiration
  - ✓ At least one Number or Special Character
  - ✓ At least 6 characters long
  - ✓ Restrictive "re-usability" of passwords
- Configurable Automatic Screen Lock mechanism during inactivity
- Database accessible only through controlled system functionality

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## 21 CFR PART 11 IMPLEMENTATION

### Audit Trail

- Comprises the Following:
  - A time-stamp
  - Field name
  - New value within the field
  - Old value within the field
  - The kind of transaction - (e.g. create, delete, modify)
  - Identification of the operator (login name)
  - An electronic signature, whenever appropriate
  - The reason for the change, whenever appropriate
- Generic Concept within PMX which can be configured for each Record Type separately - e.g. BOM, Production Procedure, ...

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## 21 CFR PART 11 IMPLEMENTATION

### Version Control

#### Work Flow Transition Graph of a Version Controlled Object

- || Represents workflow for data object
- || State transition is coupled with specific authorization and electronic signature
- || Automatic version numbering
- || Old versions that have reached certain state are kept in archive
- || System ensures that only *one* valid object at any *one* given time exists
- || Setup of different approval flows for different objects by user

```

graph TD
    Deletion[Deletion data object] --> Edit[Edit mode]
    Insertion[Insertion new data] --> Edit
    Edit -- "Author's signature" --> Test[Test]
    Edit -- "No signature" --> Approval[Approval]
    Test -- "No signature" --> Approval
    Approval -- "Stipulated period of validity and operational manager's signature" --> Released[Released]
    Released -- "Current within period of validity" --> Valid[Valid]
    Released -- "Expired period of validity" --> Archive[Archive]
    Valid -- "Expired period of validity" --> Archive
  
```

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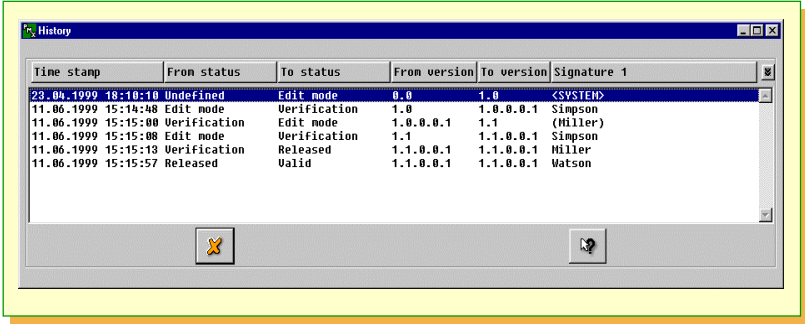


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## 21 CFR PART 11 IMPLEMENTATION

### Version Control

#### Change History of a Data Object



Time stamp	From status	To status	From version	To version	Signature 1
23.04.1999 18:10:10	Undefined	Edit mode	0.0	1.0	<SYSTEM>
11.06.1999 15:14:48	Edit mode	Verification	1.0	1.0.0.0.1	Simpson
11.06.1999 15:15:00	Verification	Edit mode	1.0.0.0.1	1.1	(Miller)
11.06.1999 15:15:08	Edit mode	Verification	1.1	1.1.0.0.1	Simpson
11.06.1999 15:15:13	Verification	Released	1.1.0.0.1	1.1.0.0.1	Miller
11.06.1999 15:15:57	Released	Valid	1.1.0.0.1	1.1.0.0.1	Watson

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## 21 CFR PART 11 IMPLEMENTATION

### Sequencing of Actions

Sequencing enforced through basic system functions and configurable mechanisms, as e.g.

- User definable master batch record
- Version graphs defining workflow from editing to archiving
- Operation workflow for recipe-based weighing

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## 21 CFR PART 11 IMPLEMENTATION

### Management and Display of Electronic Signatures

- Signature components are displayed on every paper record/screen display as appropriate
- For practical reasons, signature information can be displayed on demand

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## 21 CFR PART 11 IMPLEMENTATION

### Mandatory Signature Components

Requirement: Two distinct identification components

**User Identification Code**

Login Name

- Unique
- Associated user rights

**Password**

- Secret
- protected by password features

Please enter password:  
\*\*\*\*\*

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## 21 CFR PART 11 IMPLEMENTATION

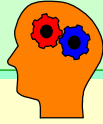
**Recommendation**

### Signature Components

**Requirement:** Two distinct identification components


**Logical Key**

user identification code (ID-Code)  
+ password  
+ differentiated user management  
and rights system



**Physical Key**

e.g. Smartcard  
with associated ID- code



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## 21 CFR PART 11 IMPLEMENTATION

### Signatures Manifestation in PMX

- Full name of signer stored within user profile and displayed in line of identification code
- Date and time always stored and displayed together with signature
- Meaning of Signatures
  - provided by context of signing, if appropriate ( e.g. within a workflow)
  - provided by explicit declaration (e.g. within report)

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## 21 CFR PART 11 IMPLEMENTATION

### Signature / Record Linking

- Electronic Signatures are linked to Electronic Records ( Data Objects) through Database Structure. DB Access is controlled through Database Management System.

### Linking Handwritten Signatures

- Control of Printouts:  
Unique, successive numbering of copies

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## 21 CFR PART 11 IMPLEMENTATION

### Uniqueness of Signatures

- PMX refuses non-unique user Identification Codes
- User accounts that have been used cannot be deleted

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## 21 CFR PART 11 IMPLEMENTATION

### Protection from Fraud

System Features to prevent Fraud:

- Secure Password Features
- Access to Database only through System Functions
- System Administrator has no knowledge of Passwords

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## 21 CFR PART 11 IMPLEMENTATION

### Password Features

- Encrypted Storage
- "Hidden" entry of password on screen
- Configurable Expiration
- At least one Number or Special Character
- At least 6 Characters long
- Restrictive "re-usability" of passwords

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## 21 CFR PART 11 IMPLEMENTATION

### Reporting for User Authorization

- Reporting functions for user / user group data available, displaying the rights of each user group and the correspondence of users to user groups

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## 21 CFR PART 11 IMPLEMENTATION

### Certifying Authorization - Implementation

- Can be bound to Transactions such as
  - Completion of an Operation step - Batch Recording, Monitoring, Weighing and Dispensing
  - Changing the Status of a Document under Version Control
  - Activation of Interaction Elements
- Certifying Rights are also Associated with either User Groups or Users

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